

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
PATENT EXAMINING OPERATION

First Named Inventor: Bandi PARTHASARADHI REDDY

Serial No: 10/509,139

Group Art Unit: 1625

Filed: 09-27-2004

Examiner: CHANG, CELIA C

Att. Docket No.: H1089/20010

Confirmation No.: 1949

For: NOVEL CRYSTALLINE FORMS OF (S)-CITALOPRAM OXALATE

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

INTRODUCTORY COMMENTS

Applicant(s) hereby request(s) review of the Final Rejection in the above-identified application.

No amendments are being filed with this request.

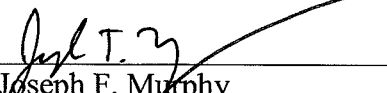
This request is being filed with a Notice of Appeal.

The review is requested for the reason(s) stated on the attached sheet(s) entitled Remarks/Arguments. The Remarks/Arguments section does not exceed five pages in length.

Respectfully submitted,

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July 10, 2008

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REMARKS/ARGUMENTS IN SUPPORT OF THE PRE-APPEAL
BRIEF REQUEST FOR REVIEW

In response to the Final Office Action dated January 17, 2008, favorable reconsideration is respectfully requested in view of the following remarks. A Notice of Appeal in compliance with 37 C.F.R. 41.31 is filed concurrently herewith.

ERRORS IN THE EXAMINER'S REJECTION UNDER 35 USC 102(b)

Claims 1-2 stand rejected under 35 USC 102(b) over US 4,943,590 (Boegesoe). This rejection is respectfully traversed.

The Examiner argues that (Office Action at page 2):

...a product made by a process is still a product. Absent of side-by-side comparison, there is no evidence that mere deletion of the solvent acetone has actually produced a "different" product. In addition, please note that every single evidence in obtaining form I (see examples 1, 2, 5) is from acetone. Even if, applicants deleted acetone from the process claims, such deletion does not obviate the anticipation since applicants' product was produced by identical process as the prior art.

However, in the Response filed November 9, 2007, it was pointed out that the claims are directed to a novel polymorphic form of (S)-citalopram, which is not crystallized from acetone, but is instead crystallized from ethyl acetate, methyl tert-butyl ether or acetonitrile. If the Examiner is arguing that the '590 Boegesoe patent inherently discloses the crystalline form of (S)-citalopram oxalate as instantly claimed, then the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. Here, the Examiner has not shown that the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.

In addition, the Examiner is incorrect in stating that there is no evidence that use of a solvent other than acetone has actually produced a "different" product, because U.S. Patent Application Publication No. 2004/0102523 (Broquaire et al.), previously cited, discloses that "[i]n this method, the nature of the solvent selected and the conditions of crystallization selected can be used to direct the preparation of any of the polymorphic forms. Therefore, the art recognizes that the use of different solvents will produce different polymorphic forms of a crystalline solid.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-4, 6-7, and 15 under 35

USC 102(b) is respectfully requested.

**ERRORS IN THE EXAMINER'S REJECTION UNDER 35 USC 112 FIRST PARAGRAPH –
WRITTEN DESCRIPTION AND ENABLEMENT**

Claims 1-2 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Claims 3-4, 6-7, 15 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The rejections are respectfully traversed.

The Examiner, citing the Kirk-Othmer reference, argues that the state of the art of polymorph recovery is highly unpredictable, and alleges that the specification, provided no description or enablement that the instantly amended process would produce form I as described by examples 1, 2 or 5 which used acetone (Office Action at pages 2-3). However, here the claims are enabled because there is not any reason to doubt the objective truth of the statements contained in the Specification for enabling support. The Specification sets forth several methods for producing Form I or Form II of (S)-citalopram oxalate, and the two novel crystalline forms of (S)-citalopram oxalate. Working Examples are also provided, as well as detailed information as to the methods. This information can be used by one of ordinary skill in the art to determine appropriate solution conditions to practice the claimed process, without undue experimentation.

Thus, given the teachings of the Specification, in light of the further experimentation carried out by Applicant using the disclosed methods, the quantity of experimentation required is not excessive in view of the subject matter of the claims. Accordingly reconsideration and withdrawal of the rejections is respectfully requested.

ERRORS IN THE EXAMINER'S REJECTION UNDER 35 USC 102(e)

Claims 10, 13, 16 stand rejected under 35 USC 102(e) over US 6,916,941 (Christensen). This rejection is respectfully traversed.

The Examiner argues that a product cannot be separated from its innate nature such as the physical properties of the product i.e. x-ray diffraction pattern, and notes that the product as disclosed by the specification was made by "any" alcoholic solvent (Office Action at page 5). However, while the '941 Christensen patent discloses a method for the manufacture of crystalline particles of (S)-citalopram oxalate by crystallization from ethanol, in the claimed method of synthesis of Form II (S)-citalopram oxalate, (S)-citalopram oxalate is not dissolved from ethanol or acetone, but from methanol or isopropyl alcohol. As set forth above, the use of different solvents will produce different crystalline forms of a

product. Therefore, the assumption that crystallization from methanol or isopropyl alcohol will yield the same polymorphic form as crystallization from acetone or ethanol has no basis in fact. In addition, claim 16 is directed to a pharmaceutical composition comprising a stable crystalline form, and thus the claimed pharmaceutical composition is not disclosed in the '941 Christensen patent.

Accordingly, reconsideration and withdrawal of the rejection of claims 10, 13, and 16 under 35 USC 102(e) is respectfully requested.

ERRORS IN THE EXAMINER'S REJECTION UNDER 35 USC 112 first paragraph

Claims 1-4, 6-7, 10, 13, 15-16 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully traversed.

The Examiner argues that (Office Action at pages 5-6):

If the Form I made by using ethyl acetate, methyl tert-butyl ether and acetonitrile is different from the product made using acetone which is supported by side-by-side comparison with the prior art product made by acetone, then, such product and process are new matter because the specification declares under oath that the same identical product was made. The Examiner further argues that if the Form II made by using methanol or isopropanol is different from the product made using ethanol which is supported by side-by-side comparison with the prior art product made by ethanol, then, such product and process are new matter because the specification declares under oath that the same identical product was made.

Here, the Examiner's reasoning is misplaced. The Specification discloses a novel polymorphic form, Form I, of (S)-citalopram, which is crystallized from ethyl acetate, methyl tert-butyl ether or acetonitrile; and also discloses a novel process of making polymorphic Form II of (S)-citalopram, which is crystallized from methanol and isopropyl alcohol. The patent specification describes the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. Applicant clearly has established possession of the invention that is now claimed. It is unclear where Applicant has "declare[d] under oath that the same identical product was made" as the prior art.

Accordingly reconsideration and withdrawal of the rejection is respectfully requested.

ERRORS IN THE EXAMINER'S REJECTION UNDER 35 USC 112 first paragraph

Claims 15-16 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. This rejection is respectfully traversed.

The Examiner argues that the specification provided no composition for which an operable carrier would maintain stability of the crystalline forms, and that the specification provided no carrier, process or how such crystalline characteristics' can be maintained in a stable environment as to be in possession of such a composition. The Examiner newly cites the Muzarraf, Jain, Doelker and Otsuke references as allegedly standing for the proposition that the state of the art evidenced that in possession of a crystalline pharmaceutical composition which maintains the crystalline form of the compound must be supported by physical measurement of such a composition with the desired crystalline characteristics being observed in the actual composition for which an operable carrier was included (Office Action at page 7).

Applicant points out that the Doelker references were provided in French, and no English translation was provided. Applicant has not had an opportunity to respond to these references. However, here the claims are enabled because there is not any reason to doubt the objective truth of the statements contained in the Specification for enabling support. The Specification discloses the manner and process for making and using the claimed invention, including working examples which show the efficacy of the claimed method. Additionally, the Specification discloses that a pharmaceutical composition comprising Form I or Form II of (S)-citalopram oxalate, and that the forms of (S)-citalopram oxalate may be formulated in a form suitable for oral administration or injection (Specification at page 3). Given the teachings of the Specification, in light of the further experimentation carried out by Applicant using the disclosed methods, the quantity of experimentation required is not excessive in view of the subject matter of the claims. The Specification sets forth several methods for producing Form I or Form II of (S)-citalopram oxalate, and the two novel crystalline forms of (S)-citalopram oxalate. Working Examples are also provided, as well as detailed information as to the methods. This information can be used by one of ordinary skill in the art to determine appropriate solution conditions to practice the claimed process, without undue experimentation.

Accordingly, reconsideration and withdrawal of the rejection of claims 15-16 under 35 USC 112 first paragraph is respectfully requested.

ERRORS IN THE EXAMINER'S REJECTION UNDER 35 USC 103(a)

Claims 1-16 stand rejected under 35 USC 103(a) over Boegesoe et al. '590 or Christensen et al. '941 in view of Cheronis supplemented with Sanches '613, Rock et al. '011 or Humbel et al. '686. This rejection is respectfully traversed.

The Examiner argues that one skilled in the art is deemed to be aware of all the alternative choices of solvents for crystallization of (S)-citalopram oxalate, and the motivation of obtaining purer, better crystals would have suggested to one skilled in the art to employ those alternative choices of solvents explicitly disclosed by Sanches, Rock or Humbel during crystallization of citalopram oxalate with the expectation that crystalline forms would be resulted, and that basis of an advantage in terms of stability, formulation, solubility.....etc. (see Brittain p.2, 185) (Office Action at page 7-8).

Here, not every element of the claims is taught or suggested in the combination of the '590 Boegesoe and '941 Christensen in view of Cheronis supplemented with '613 Sanches, '011 Rock or '686 Humble references. The instant claims are directed to novel polymorphic forms of (S)-citalopram oxalate, and methods of making them. However, the prior art relied upon by the examiner does not teach or suggest the specific polymorphs as claimed by Applicant. The Examiner failed to demonstrate that the prior art even recognized that the claimed compound exists in different polymorphic forms, or that there is a known or obvious way to manufacture the specific polymorphic form claimed. The Examiner admits that the combination of references may not teach or suggest the polymorphic forms as claimed "[i]n other words, even if the prima facie modified process produced a different crystalline form it is obvious absent of comparative data." (Office Action at page 7-8).

The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic (see above). Here, the Examiner has assumed, without providing any evidence, that the methods of producing (S)-citalopram oxalate in the '590 Boegesoe patent can be altered to produce the claimed polymorphs. However, there is no basis for this assumption because, as set forth above, the use of different solvents will produce different crystalline forms of a product (see above). Therefore, the assumption that crystallization of (S)-citalopram oxalate from ethyl acetate, methyl tert-butyl ether, acetonitrile, methanol or isopropyl alcohol will yield the same polymorphic forms as crystallization from acetone or ethanol has no basis in fact.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-16 under 35 USC 103(a) is respectfully requested.

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Accordingly, the Pre-Appeal Brief Conference Panel is respectfully requested to withdraw the appealed rejection(s) and pass this application on to issuance.